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Risk factors for metachronous colorectal cancer following a primary colorectal cancer: A prospective cohort study

Harindra Jayasekara[1,2], **Jeanette C. Reece**[1], **Daniel D. Buchanan**[1,3], **Christophe Rosty**[3,4], **S. Ghazaleh Dashti**[1], **Driss Ait Ouakrim**[1], **Ingrid M. Winship**[5,6], **Finlay A. Macrae**[5,6,7], **Alex Boussioutas**[5,8], **Graham G. Giles**[1,2], **Dennis J. Ahnen**[9], **Jan Lowery**[10], **Graham Casey**[11], **Robert W. Haile**[12], **Steven Gallinger**[13], **Loic Le Marchand**[14], **Polly A. Newcomb**[15,16], **Noralane M. Lindor**[17], **John L. Hopper**[1], **Susan Parry**[18], **Mark A. Jenkins**[1], and **Aung Ko Win**[1]

[1]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia [2]Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Victoria, Australia [3]Colorectal Oncogenomics Group, Genetic Epidemiology Laboratory, Department of Pathology, The University of Melbourne, Parkville, Victoria, Australia [4]University of Queensland, School of Medicine, Herston, Queensland, Australia [5]Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia [6]Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Parkville, Australia [7]Colorectal Medicine and Genetics, Royal Melbourne Hospital, Parkville, Victoria, Australia [8]Cancer Genomics and Predictive Medicine, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia [9]Department of Medicine, University of Colorado School of Medicine, Denver, Colorado, USA [10]Department of Epidemiology, University of Colorado School of Public Health, Denver, Colorado, USA [11]Department of Preventive Medicine, Keck School of Medicine and Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California, USA [12]Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University, California, USA [13]Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada [14]University of Hawaii Cancer Center, Honolulu, Hawaii, USA [15]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA [16]School of Public Health, University of Washington, Seattle, Washington, USA [17]Department of Health Science Research, Mayo Clinic Arizona, Scottsdale, Arizona, USA [18]New Zealand Familial Gastrointestinal Cancer Service, Auckland, New Zealand

Correspondence to: Dr Aung Ko Win, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, Level 3, 207 Bouverie Street, The University of Melbourne VIC 3010 Australia, Phone: +61 3 9035 8238; Fax: +61 3 9349 5815; awin@unimelb.edu.au.

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Abstract

Individuals diagnosed with colorectal cancer (CRC) are at risk of developing a metachronous CRC. We examined the associations between personal, tumour-related and lifestyle risk factors, and risk of metachronous CRC. A total of 7,863 participants with incident colon or rectal cancer who were recruited in the USA, Canada and Australia to the Colon Cancer Family Registry during 1997–2012, except those identified as high-risk e.g. Lynch syndrome, were followed up approximately every 5 years. We estimated the risk of metachronous CRC, defined as the first new primary CRC following an interval of at least one year after the initial CRC diagnosis. Observation time started at the age at diagnosis of the initial CRC and ended at the age at diagnosis of the metachronous CRC, last contact or death whichever occurred earliest, or were censored at the age at diagnosis of any metachronous colorectal adenoma. Cox regression was used to derive hazard ratios (HRs) and 95% confidence intervals (CIs). During a mean follow-up of 6.6 years, 142 (1.81%) metachronous CRCs were diagnosed (mean age at diagnosis 59.8; incidence 2.7/1000 person-years). An increased risk of metachronous CRC was associated with the presence of a synchronous CRC (HR=2.73; 95% CI: 1.30–5.72) and the location of cancer in the proximal colon at initial diagnosis (compared with distal colon or rectum, HR=4.16; 95% CI: 2.80–6.18). The presence of a synchronous CRC and the location of the initial CRC might be useful for deciding the intensity of surveillance colonoscopy for individuals diagnosed with CRC.

Keywords

Colorectal cancer; metachronous; risk factors

Introduction

Individuals diagnosed with a colorectal cancer (CRC) are at increased risk of developing a metachronous CRC (a new primary CRC that is not a recurrence or a metastatic deposit of the initial lesion) in the remaining part of the large bowel later in life.[1] This has been reported especially in North America, Europe, Australia and New Zealand, the regions of the world with the highest incidence of CRC, where prognosis for individuals affected by an initial CRC has improved in recent decades.[2] The risk of developing a metachronous CRC in the five years following curative surgical resection of the bowel for the initial CRC is around 2%–12% depending on the intensity of follow-up.[3–5]

An individual's risk of developing a metachronous CRC has important clinical implications on the extent of the bowel resection for the initial CRC and the frequency of endoscopic surveillance of the remaining bowel.[6] The extent of the bowel resection, i.e. segmental versus extensive, is likely to modify the risk of developing a metachronous CRC because of the differences in length of the remaining bowel. This is exemplified by individuals with Lynch syndrome whose metachronous CRC risk depends on the type of surgery and the length of bowel removed for the initial colon cancer.[7] The functional consequence of an increase in bowel movement frequency and the possible negative impact on quality of life following more extensive surgery need to be balanced against the reduction in the risk of metachronous CRC.[8] Regardless, surveillance of the remaining colon and rectum is required after most surgery (except total proctocolectomy). An initial follow-up colonoscopy is

recommended after one year, and if this colonoscopy is clear, the next colonoscopy is recommended at three years.[6, 9] More intense colonoscopy surveillance (i.e., at shorter intervals) is advocated for high-risk individuals[6] but the optimal interval for surveillance colonoscopy is unclear due to a lack of strong evidence comparing the effectiveness of different surveillance regimens and an insufficient understanding of the predictors of metachronous CRC risk.

If stratification of individuals based on their risk for metachronous CRC could be made routinely, the reduction of metachronous CRC incidence by targeted surveillance colonoscopy would become cost-effective.[10] Two previous systematic reviews have examined risk factors for metachronous colorectal adenoma or cancer[6, 11] but have assessed only the features of the first diagnosis of CRC or adenoma and not individual's lifestyle factors. In the current study, we used a prospective cohort of adults diagnosed with CRC to examine associations between personal, tumour-related features and lifestyle factors and the risk of metachronous CRC.

Material and methods

Study sample

Individuals included in the current study were probands diagnosed with incident colon or rectal cancer from the Colon Cancer Family Registry. Between 1997 and 2012, they were recruited regardless of a family history of cancer via state or regional population cancer registries in USA (Washington, California, Arizona, Minnesota, Colorado, New Hampshire, North Carolina and Hawaii), Australia (Victoria), and Canada (Ontario) or recruited via family cancer clinics in the USA (Mayo Clinic, Rochester, Minnesota, and Cleveland Clinic, Cleveland, Ohio), Ontario (Canada), Australia (Melbourne, Adelaide, Perth, Brisbane, Sydney) and New Zealand (Auckland).[12] Informed consent was obtained from all study participants, and the study protocol was approved by the institutional research ethics review board at each centre.

Of the 9,916 persons initially identified from the Colon Cancer Family Registry with a CRC and who had returned an epidemiologic questionnaire, the following were excluded from analysis: those with Lynch syndrome (n=561), monoallelic or biallelic *MUTYH* mutation carriers (n=208), those diagnosed with a cancer of the appendix (n=65), those with total resection of colon and rectum (n=5), those with no follow-up (n=105), those with an interval of more than 2 years from diagnosis of CRC to enrolment in the study (n=1,100), those who had completed baseline data collection questionnaire prior to initial diagnosis (n=8) and those missing enrolment date (n=1). None of the remaining 7,863 persons included in this analysis had been diagnosed with familial adenomatous polyposis.

Data collection

Data on demographics, race/ethnicity, personal and familial history of cancer, medical history, reproduction, diet, alcohol, tobacco, body weight and height were collected via standardized personal interviews, telephone interviews and/or mailed questionnaires (available at: http://www.coloncfr.org/questionnaires).[12] Participants were followed up

approximately every 5 years after recruitment into the study to update information across all study centres. Reported cancer diagnoses and age at diagnosis were confirmed, where possible, using pathology reports, medical records, cancer registry reports and death certificates. The anatomic location and histology of the tumours were coded and stored using International Classification of Diseases for Oncology, third edition (ICD-O-3).[13] Permission to access tumour tissue was requested from all participants diagnosed with CRC and blood sample from all participants. Vital status, cause of death and date of death were ascertained through contact with next-of-kin and/or linkage with population-based registries.

CRC pathology review

CRCs were reviewed by pathologists at each study centre of the Colon Cancer Family Registry and assessed for features including histologic grade (low or high grade) and synchronous CRCs (present or absent). Low grade was defined as adenocarcinoma with ≥50% gland formation and high grade as adenocarcinoma with <50% gland formation. Diagnosis disease stage was collected from state/provincial cancer registry information and/or from clinical/pathology records. When stage data were available both from registries and clinical/pathology records, the latter took precedence. Harmonized summary stage data were derived according to American Joint Commission on Cancer (AJCC) Tumour Node Metastasis (TNM) criteria[14] or converted from SEER summary stage to TNM summary stage using an algorithm.[15] A metachronous CRC was defined as a new primary colon or rectal cancer diagnosed at least one year after the first diagnosis of primary colon or rectal cancer.

Tumour molecular characterization

Colorectal tumours were characterized for mismatch repair (MMR)-deficiency by microsatellite instability (MSI) using a ten-marker panel and/or by immunohistochemistry (IHC) for the four MMR proteins. Tumours were classified as MMR-deficient if they were MSI-high (≥30% or more of the markers show instability) and/or showed loss of expression of one or more of the MMR proteins by IHC; and MMR-proficient if they were microsatellite stable (no unstable markers) or MSI-low (<30% unstable markers) and/or showed normal expression of all four MMR proteins by IHC.

Statistical analysis

Observation time started at the age at diagnosis of the initial CRC and ended at the age at diagnosis of the metachronous CRC (n=142), last contact (n=4,986) or death (n=2,459) whichever occurred earliest, or were censored at the age at polypectomy of metachronous colorectal adenoma (n=276) given that polypectomy reduces the risk of CRC. In this analysis, exposures comprised potential risk factors including demographic, genetic and lifestyle characteristics as well as tumour-related features of the initial CRC (listed in Table 1) and the outcome was the incidence of metachronous CRC. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models to estimate the associations between potential risk factors and the risk of metachronous CRC. Tests based on Schoenfeld residuals showed no evidence that proportional hazard assumptions were violated. Wald tests were used to assess linear trends.

Frequency of surveillance colonoscopy after surgery for initial CRC, but before the diagnosis of metachronous CRC, was estimated from the self-reported questionnaire data. The frequency of surveillance colonoscopy was assumed to be distributed uniformly in the period between first and last age of colonoscopy.

We devised a multiple imputation model to impute values for missing data that occurred for some tumour pathology features, alcohol consumption and interval of surveillance colonoscopy. The missing data were assumed to be at random. The model included predictor variables, the outcome variable and additional variables that we considered may increase the plausibility of the missing at random assumption in order to improve the imputation process. We chose 10 sets based on recommendations that the number of sets should approximate the percentage of participants with some missing data.[16] Alcohol intake was imputed using predictive mean matching, stage of first diagnosis of CRC and surveillance colonoscopy interval were imputed using ordinal logistic regression, and the other pathology features were imputed using logistic regression. Missing values were sampled and replaced with a set of plausible values randomly drawn from their predicted distribution based on the other observed variables, thus creating 10 completed data sets. Cox proportional hazard regression models were run separately for each imputed data set and estimates of the predictor variables were combined using the programs written by Carlin et al.[17] We compared the estimates of association from models using the imputed missing data with the estimates from complete-case analyses.

A sensitivity analysis was conducted to investigate whether censoring at the age at diagnosis of colorectal adenoma changed associations between potential risk factors and metachronous CRC risk. All statistical tests were two sided. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX).

Results

In this cohort of 7,863 individuals diagnosed with CRC (5,316 colonic; 2,547 rectal), 142 (1.81%) were diagnosed with a metachronous CRC (mean age 59.8 (standard deviation, SD 12.7) years at diagnosis; incidence 2.7 per 1000 person-years) during a mean follow-up of 6.6 (minimum 1; maximum 16) years. Of them, 7,413 (94.3%) were from population-based sources and 1,689 (21.5%) had at least one first-degree relative affected with CRC. The mean time interval between initial CRC and metachronous CRC diagnoses was 4.1 (SD 3.4) years. The cumulative risk of metachronous CRC was 1.59% at 5 years, 2.36% at 10 years, and 3.57% at 15 years post-cancer resection (Figure 1A). The initial CRC site was approximately equally distributed across the proximal colon (32.6%), distal colon (30.8%) and rectum (32.4%), and 329 (4.2%) were coded as unspecified site of the colon. Of the 142 metachronous CRCs, 51 (35.9%) were located in the proximal colon, 27 (19.1%) in the distal colon and 32 (22.5%) in the rectum, and 32 (22.5%) in an unspecified site of the colon.

Demographic, lifestyle and tumour features of the initial CRC stratified by cancer site (proximal colon, distal colon/rectum, unspecified site of colon) are shown in Table 1. The study sample consisted of approximately equal numbers of men and women overall who

were predominantly aged 50 years or over and nearly half were never smokers. More than one-fifth of the study population had a first-degree family history of CRC. Of individuals for whom treatment data were available, 58.0% (n=1,370) reported having chemotherapy while 33.4% (n = 499) reported having radiation therapy. Of 4,891 CRCs with available tumour MMR status, 88% (n=4,327) were MMR-proficient.

The presence of a synchronous CRC at first diagnosis was associated with an increased risk of metachronous CRC (HR=2.73; 95% CI: 1.30–5.72) (Table 2; Figure 1B). The proximal colon location of the first diagnosis of CRC was associated with a higher risk of metachronous CRC (HR=4.16; 95% CI: 2.80–6.18) compared with distal colon or rectum (Table 2; Figure 1C). An elevated risk of metachronous CRC associated with a tumour MMR-deficiency status in the univariable model was not evident when adjusted for other covariates (Table 2). An interval of over 2 years for surveillance colonoscopy was inversely associated with the risk of metachronous CRC compared with annual colonoscopy (Table 2). There was no evidence for an association between other tumour features, personal features, and any of the measured lifestyle factors and the risk of metachronous CRC (Table 2). No evidence was found for associations between female reproductive factors (parity, hormonal contraceptive use and hormonal replacement therapy) and the risk of metachronous CRC for women when included in a multivariable model (details not shown).

In the complete case analysis, the directions of associations were consistent with results from the main analysis using imputed data except for diabetes mellitus (Supplementary Table 1). Individuals with diabetes mellitus had a higher risk of metachronous CRC than those without diabetes (HR=3.77; 95% CI: 1.15–12.3) (Supplementary Table 1). The results did not change materially when an analysis was conducted without censoring at the age at diagnosis of metachronous colorectal adenoma (Supplementary Table 2).

Discussion

In this prospective cohort study, we observed that the presence of a synchronous CRC and the location of the initial CRC in the proximal colon were associated with an increased risk of metachronous CRC. There was no evidence for an association between environmental factors measured before the initial CRC and the risk of metachronous CRC.

The strengths of the current study include its large sample size, the availability of extensive demographic, clinical and lifestyle data, and a substantial follow-up which enabled us to examine a wide range of potential risk factors for metachronous CRC. Nonetheless, there were some limitations. First, this study lacked detailed data on treatment (including the extent of colorectal resection) and complications of treatment which were not able to be adjusted for in the multivariable analysis. However, considering the uniformity in treatment options for those suitable for surveillance colonoscopy,[6] our results may not have changed substantially even if treatment data were available. Second, we did not have information on the quality of the surveillance colonoscopy as well as the exact timing of the surveillance colonoscopy for each individual. Our finding that a longer interval between colonoscopy may be inversely associated with the risk of metachronous CRC could be interpreted that more frequent surveillance colonoscopy results in greater metachronous CRC detection.

Finally, although missing data could potentially have been a limitation, a comprehensive imputation procedure was carried out along with a sensitivity analysis comparing risk estimates from imputed and complete-case analyses.

The incidence of metachronous CRC occurrence estimated by our analysis was 1.81% (142 metachronous cancers/7,863 initial cancers) which is closer to the lower end of the range reported in the literature (0.6–9%).[18] These estimates could be affected by the length of survival and length of follow-up. Similar to our finding, previous studies that examined tumour location as a risk factor observed that the initial cancer in the proximal colon is associated with a higher risk of metachronous CRC.[19, 20] The 2.2% prevalence of synchronous CRC in our cohort was comparable with 2–7% reported elsewhere.[3, 21] Our finding of the presence of synchronous CRC being a risk factor for metachronous CRC is also consistent with the previous reports.[3, 18, 22]

Chromosomal instability (CIN), MSI, and CpG island methylator phenotype (CIMP) are the three molecular pathways explaining the pathogenesis of CRC.[23] Arain et al.[24] reported that interval cancers in the colon were 2.5-times more likely to demonstrate CIMP, were 2.7-times more likely to demonstrate MSI, and also had a 2-fold higher incidence in the proximal colon. Similarly, in a study using data from the Nurses' Health Study and the Health Professionals Follow-up Study, Nishihara et al. found that CRC diagnosed within 5 years after screening colonoscopy was more likely to be characterized by CIMP, MSI and high-level LINE-1 methylation than cancer diagnosed more than 5 years after colonoscopy.[25] While evidence is still lacking that the CIMP pathway could independently play a role in accelerated tumour growth, our evidence of a greater risk of metachronous cancer for individuals with an initial cancer in the proximal colon could well be related to CIMP-related interval cancers. We were not able to stratify our analysis by tumour site (e.g. initial cancer in the proximal colon and metachronous cancer in the distal colon/rectum) due to the relatively small number of metachronous CRCs available by anatomical site (51 in the proximal colon, 59 in the distal colon/rectum).

Identification and removal of adenomatous polyps through surveillance colonoscopy reduce the risk of metachronous CRC.[6] The clinical guidelines suggest surveillance colonoscopies at intervals of 1, 3 and 5 years if the findings continue to be normal.[6] Our findings suggest that individuals diagnosed with a CRC in the proximal colon and those with a synchronous CRC might be considered for more intense surveillance colonoscopy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation

AJCC	American Joint Commission on Cancer
CI	confidence interval
CIMP	CpG island methylator phenotype
CIN	chromosomal instability
CRC	colorectal cancer
HR	hazard ratio
ICD-O	International Classification of Diseases for Oncology
IHC	immunohistochemistry
MMR	mismatch repair
MSI	microsatellite instability

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Novelty and Impact

The location of the initial colorectal cancer in the proximal colon and the presence of a synchronous colorectal cancer were associated with an increased risk of metachronous colorectal cancer thus highlighting their important when deciding on the intensity of surveillance colonoscopy whereas personal, lifestyle factors and female reproductive factors were not associated.

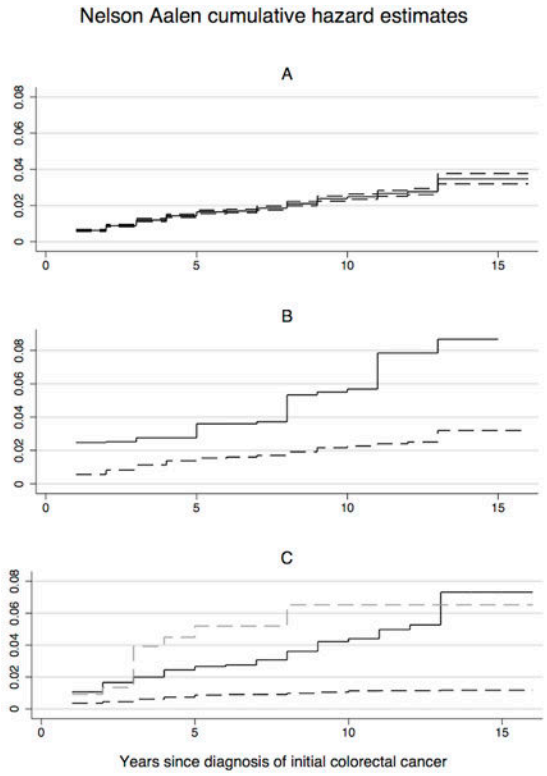

Figure 1.

Nelson–Aalen estimate of the cumulative hazard rate function for incidence of metachronous colorectal cancer for individuals with colorectal cancer. A, overall (solid), 95% confidence limits (dashed); B, synchronous colorectal cancer present (solid), synchronous colorectal cancer absent (dashed); C, proximal colon (solid), distal colon/ rectum (black dashed), unspecified colon (gray dashed).

Table 1

Baseline Characteristics of Individuals with Colorectal Cancer (CRC): Colon Cancer Family Registry, 1997 to 2012

	Initial cancer site[a]			Total (*n*=7,863)
	Proximal colon (*n*=2562)	Distal colon/rectum (*n*=4,972)	Unspecified colon (*n*=329)	
	n (%)	*n* (%)	*n* (%)	*n* (%)
Age at initial diagnosis, years				
<50	741 (28.9)	2,117 (42.6)	132 (40.1)	2,990 (38.0)
≥50	1,821 (71.1)	2,855 (57.4)	197 (59.9)	4,873 (62.0)
Mean age (years)	58.0	53.9	54.9	55.3
Colon Cancer Family Registry site				
Cancer Care Ontario, Toronto, Canada	615 (24.0)	1,287 (25.9)	37 (11.3)	1,939 (24.7)
University of Southern California Consortium	572 (22.3)	875 (17.6)	230 (69.9)	1,677 (21.3)
University of Melbourne, Australia	228 (8.9)	568 (11.4)	10 (3.0)	806 (10.2)
University of Hawaii, Honolulu, HI	142 (5.5)	303 (6.1)	1 (0.3)	446 (5.7)
Mayo Clinic, Rochester, MN	168 (6.7)	424 (8.5)	16 (4.9)	608 (7.7)
Fred Hutchinson Cancer Research Center	767 (29.9)	1,420 (28.6)	29 (8.8)	2,216 (28.2)
Cancer Prevention Institute of California	70 (2.7)	95 (1.9)	6 (1.8)	171 (2.2)
Source of ascertainment				
Population-based	2,407 (93.9)	4,699 (94.5)	307 (93.3)	7,413 (94.3)
Clinic-based	155 (6.1)	273 (5.5)	22 (6.7)	450 (5.7)
Sex				
Male	1,167 (45.5)	2,633 (53.0)	169 (51.4)	3,969 (50.5)
Female	1,395 (54.5)	2,339 (47.0)	160 (48.6)	3,894 (49.5)
First-degree family history of CRC				
No	1,948 (76.0)	3,970 (79.9)	256 (77.8)	6,174 (78.5)
Yes	614 (24.0)	1,002 (20.1)	73 (22.2)	1,689 (21.5)
Cigarette smoking status[b]				
Never	1,164 (45.4)	2,194 (44.1)	164 (49.8)	3,522 (44.8)
Former	1,121 (43.8)	2,212 (44.5)	126 (38.3)	3,459 (44.0)
Current	277 (10.8)	566 (11.4)	39 (11.9)	882 (11.2)
Alcohol intake				
Abstainer	813 (31.7)	1,299 (26.1)	105 (31.9)	2,217 (28.2)
<1 drink/day	505 (19.7)	1,097 (22.1)	54 (16.4)	1,656 (21.1)
1–<2 drinks/day	251 (9.8)	517 (10.4)	30 (9.1)	798 (10.1)
2–<3 drinks/day	79 (3.1)	279 (5.6)	17 (5.2)	375 (4.8)
≥3 drinks/day	182 (7.1)	491 (9.9)	42 (12.8)	715 (9.1)
Missing	732 (28.6)	1,289 (25.9)	81 (24.6)	2,102 (26.7)
BMI recent[c], kg/m^2				
<18.5	61 (2.4)	150 (3.0)	27 (8.2	238 (3.0)

	Initial cancer site[a]			Total (*n*=7,863)
	Proximal colon (*n*=2562)	Distal colon/rectum (*n*=4,972)	Unspecified colon (*n*=329)	
	n (%)	*n* (%)	*n* (%)	*n* (%)
18.5–<25	900 (35.1)	1,687 (33.9)	117 (35.6)	2,704 (34.4)
25–<30	928 (36.2)	1,844 (37.1)	106 (32.2)	2,878 (36.6)
≥30	673 (26.3)	1,291 (26.0)	79 (24.0)	2,043 (26.0)
BMI at age 20 years[d], kg/m^2				
<18.5	313 (12.2)	467 (9.4)	94 (28.6)	874 (11.1)
18.5–<25	1,671 (65.2)	3,340 (67.2)	175 (53.2)	5,186 (66.0)
25–<30	418 (16.3)	821 (16.5)	39 (11.8)	1,278 (16.2)
≥30	160 (6.3)	344 (6.9)	21 (6.4)	525 (6.7)
Diabetes mellitus[e]				
No	2,197 (85.7)	4,416 (88.8)	270 (82.1)	6,883 (87.5)
Yes	365 (14.3)	556 (11.2)	59 (17.9)	980 (12.5)
Aspirin intake				
No	1,739 (67.9)	3,664 (73.7)	237 (72.0)	5,640 (71.7)
Yes	823 (32.1)	1,308 (26.3)	92 (28.0)	2,223 (28.3)
Ibuprofen intake				
No	2,156 (84.1)	4,150 (83.5)	286 (86.9)	6,592 (83.8)
Yes	406 (15.9)	822 (16.5)	43 (13.1)	1,271 (16.2)
Multivitamin supplement intake				
No	1,216 (47.5)	2,481 (49.9)	152 (46.2)	3,849 (49.0)
Yes	1,346 (52.5)	2,491 (50.1)	177 (53.8)	4,014 (51.0)
Calcium supplement intake				
No	1,848 (72.1)	3,775 (75.9)	261 (79.3)	5,884 (74.8)
Yes	714 (27.9)	1,197 (24.1)	68 (20.7)	1,979 (25.2)
Parity[f]				
0	165 (11.8)	274 (11.7)	20 (12.5)	459 (11.8)
1–2	441 (31.6)	804 (34.4)	57 (35.6)	1,302 (33.4)
≥3	789 (56.6)	1,261 (53.9)	83 (51.9)	2,133 (54.8)
Hormonal contraceptive use for at least 1 year[f]				
No	641 (46.0)	903 (38.6)	73 (45.6)	1,617 (41.5)
Yes	754 (54.0)	1,436 (61.4)	87 (54.4)	2,277 (58.5)
Use of hormonal replacement therapy for at least 6 months[g]				
No	567 (54.1)	901 (58.6)	79 (69.3)	1,547 (57.3)
Yes	481 (45.9)	637 (41.4)	35 (30.7)	1,153 (42.7)
Surveillance colonoscopy interval[h]				
≤1 year	94 (3.7)	180 (3.6)	13 (3.9)	287 (3.6)
>1–2 years	327 (12.8)	726 (14.6)	47 (14.3)	1,100 (14.0)
>2–3 years	261 (10.2)	525 (10.6)	26 (7.9)	812 (10.3)
>3 years	594 (23.2)	1,126 (22.6)	46 (14.0)	1,766 (22.5)

	Initial cancer site[a]			Total (*n*=7,863)
	Proximal colon (*n*=2562)	Distal colon/rectum (*n*=4,972)	Unspecified colon (*n*=329)	
	n (%)	*n* (%)	*n* (%)	*n* (%)
No colonoscopy	32 (1.2)	48 (1.0)	0 (0.0)	80 (1.0)
Missing	1,254 (48.9)	2,367(47.6)	197 (59.9)	3,818 (48.6)
Synchronous CRC				
No	1,921 (75.0)	3,798 (76.4)	174 (52.9)	5,893 (75.0)
Yes	91 (3.5)	77 (1.5)	6 (1.8)	174 (2.2)
Missing	550 (21.5)	1,097 (22.1)	149 (45.3)	1,796 (22.8)
Synchronous adenoma				
No	1,031 (40.2)	1,966 (39.5)	75 (22.8)	3,072 (39.1)
Yes	359 (14.0)	794 (16.0)	40 (12.2)	1,193 (15.2)
Missing	1,172 (45.8)	2,212 (44.5)	214 (65.0)	3,598 (45.7)
TNM stage				
I	204 (8.0)	523 (10.5)	10 (3.0)	737 (9.4)
II	297 (11.6)	378 (7.6)	6 (1.8)	681 (8.7)
III	323 (12.6)	544 (10.9)	8 (2.4)	875 (11.1)
IV	148 (5.8)	268 (5.4)	21 (6.4)	437 (5.6)
Missing	1,590 (62.1)	3,259 (65.6)	284 (86.3)	5,133 (65.3)
Tumour grade				
Low	1,300 (50.7)	2,936 (59.0)	91 (27.7)	4,327 (55.0)
High	427 (16.7)	476 (9.6)	22 (6.7)	925 (11.8)
Missing	835 (32.6)	1,560 (31.4)	216 (65.6)	2,611 (33.2)
Tumour mismatch repair status				
Proficient	1,197 (46.7)	3,059 (61.5)	52 (15.8)	4,308 (54.8)
Deficient	442 (17.3)	137 (2.8)	4 (1.2)	583 (7.4)
Missing	923 (36.0)	1,776 (35.7)	273 (83.0)	2,972 (37.8)
Chemotherapy				
Yes	412 (16.1)	945 (19.0)	13 (3.9)	1,370 (17.4)
No	337 (13.1)	643 (12.9)	12 (3.7)	992 (12.6)
Missing	1,813 (70.8)	3,384 (68.1)	304 (92.4)	5,501 (70.0)
Radiotherapy				
Yes	16 (0.6)	479 (9.6)	4 (1.2)	499 (6.3)
No	409 (16.0)	572 (11.5)	16 (4.9)	997 (12.7)
Missing	2,137 (83.4)	3,921 (78.9)	309 (93.9)	6,367 (81.0)

[a] According to International Classification of Diseases for Oncology, Third Edition anatomical site codes: C18.0, C18.2, C18.3, C18.4 (proximal colon); C18.5, C18.6, C18.7, C19.9, C20.9 (distal colon/rectum); C18.8, C18.9, C26.0 (unspecified colon).

[b] Cigarette smoking was defined as ever smoking one cigarette per day for 3 months or longer. Current smoking was indicated when persons reported smoking in the referent period (defined as two years prior to enrolment); former smoking was indicated when persons stopped smoking before the referent period.

[c] Derived from pre-diagnosis recent body weight (defined as “weight 2 years prior to enrolment”) in kg divided by height in meters squared.

[d] Derived from body weight at age 20 years in kg divided by height in meters squared.

[e] Self-report that diabetes mellitus was diagnosed by a physician, excluding gestational diabetes.

[f] Numbers add up to women.

[g] Numbers add up to menopausal women.

[h] Derived from time since initial colorectal cancer diagnosis divided by number of post-diagnosis surveillance colonoscopies.

Table 2

Hazard ratios (HR) and 95% confidence intervals (CI) for associations between personal factors, initial colorectal cancer (CRC) tumour pathology features, lifestyle factors and surveillance interval and the risk of metachronous CRC

	Cases/Person-years	Univariable HR (95% CI)	*p*-value[a]	Multivariable HR (95% CI)	*p*-value[a]
Personal factors					
Age at initial diagnosis					
<50 years	52/18,336	1		–	
≥50 years	90/33,706	0.97 (0.69–1.37)	0.88	–	–
Per 10-year increment	142/52,042	1.01 (0.88–1.17)	0.85	0.93 (0.79–1.10)	0.41
Sex					
Male	63/25,574	1		1	
Female	79/26,468	1.23 (0.88–1.71)	0.22	1.26 (0.84–1.89)	0.26
First-degree family history of CRC					
No	101/39,857	1		1	
Yes	41/12,185	1.36 (0.95–1.96)	0.10	1.20 (0.83–1.75)	0.33
Initial tumour features					
Synchronous CRC[b]					
No	109/40,713	1		1	
Yes	9/1,039	2.80 (1.38–5.69)	0.005	2.73 (1.30–5.72)	0.008
Synchronous adenoma[b]					
No	62/20,331	1		1	
Yes	27/8,984	1.04 (0.64–1.69)	0.87	0.80 (0.48–1.35)	0.40
Site of initial tumour[c]					
Proximal colon	85/16,697	3.77 (2.62–5.41)	<0.001	4.16 (2.80–6.18)	<0.001
Distal colon/rectum	45/33,718	1		1	
Unspecified colon	12/1,627	5.02 (2.65–9.50)	<0.001	6.10 (3.08–12.10)	<0.001
TNM stage[b]					
I	19/6,379	1		1	
II	13/5,515	0.83 (0.45–1.56)		0.67 (0.34–1.33)	
III	15/6,443	0.82 (0.41–1.61)		0.51 (0.21–1.25)	

	Cases/Person-years	Univariable HR (95% CI)	*p*-value[a]	Multivariable HR (95% CI)	*p*-value[a]
IV	6/1,664	0.74 (0.36–1.52)	0.43[j]	0.40 (0.12–1.32)	0.11[j]
Tumour grade[b]					
Low	94/30,447	1		1	
High	16/5,841	0.85 (0.52–1.39)	0.52	0.75 (0.44–1.29)	0.30
Tumour mismatch repair status[b]					
Proficient	89/30,718	1		1	
Deficient	20/4,656	1.58 (0.96–2.59)	0.07	0.87 (0.51–1.46)	0.59
Lifestyle factors					
Smoking status[d]					
Never	58/23,479	1		1	
Former	66/23,231	1.15 (0.81–1.64)		1.25 (0.86–1.82)	
Current	18/5,332	1.33 (0.78–2.25)	0.26[j]	1.32 (0.75–2.31)	0.23[j]
Alcohol intake[b]					
Per 14 g/day increment	103/38,536	0.99 (0.92–1.08)	0.92	0.99 (0.89–1.12)	0.99
BMI recent[e], kg/m^2					
Per 5 kg/m^2	142/52,042	0.99 (0.97–1.03)	0.81	0.99 (0.97–1.02)	0.69
BMI at age 20 years[f], kg/m^2					
Per 5 kg/m^2	150/52,030	0.99 (0.97–1.02)	0.61	0.99 (0.97–1.01)	0.55
Diabetes mellitus[g]					
No	128/46,115	1		1	
Yes	14/5,927	0.83 (0.48–1.44)	0.50	0.79 (0.45–1.41)	0.43
Aspirin intake					
No	103/36,765	1		1	
Yes	39/15,277	0.92 (0.64–1.33)	0.67	0.89 (0.60–1.31)	0.55
Ibuprofen intake					
No	119/43,432	1		1	
Yes	23/8,610	0.98 (0.63–1.53)	0.93	0.97 (0.62–1.53)	0.90
Multivitamin supplement intake					
No	64/24,942	1		1	

	Cases/Person-years	Univariable HR (95% CI)	*p*-value[a]	Multivariable HR (95% CI)	*p*-value[a]
Yes	78/27,100	1.21 (0.85–1.70)[h]	0.29	1.24 (0.86–1.78)	0.24
Calcium supplement intake					
No	107/37,886	1		1	
Yes	35/14,156	0.90 (0.61–1.32)	0.58	0.77 (0.51–1.18)	0.23
Surveillance interval[b,i]					
≤1 year	12/2,006	1		1	
>1–2 years	31/9,181	0.72 (0.38–1.35)		0.74 (0.39–1.38)	
>2–3 years	7/7,496	0.32 (0.13–0.76)		0.34 (0.15–0.77)	
>3 years	42/16,716	0.49 (0.27–0.89)	0.06[j]	0.56 (0.29–1.06)	0.08[j]
No colonoscopy	1/913	0.29 (0.05–1.77)		0.22 (0.03–1.74)	

Multivariable model included personal factors, initial tumour pathology features, lifestyle factors and surveillance interval as shown in the table, and country of data collection (United States; Canada; Australia). HRs reported using BMI recent in the multivariable model; HR for BMI at 20 years reported using BMI at 20 years in place of BMI recent in the model.

[a] Wald P-value.

[b] HRs calculated using imputed values from multiple imputation method for missing values.

[c] According to International Classification of Diseases for Oncology, Third Edition anatomical site codes: C18.0, C18.2, C18.3, C18.4 (proximal colon); C18.5, C18.6, C18.7, C19.9, C20.9 (distal colon/rectum); C18.8, C18.9, C26.0 (unspecified colon).

[d] Cigarette smoking was defined as ever smoking one cigarette per day for 3 months or longer. Current smoking was indicated when persons reported smoking in the referent period (defined as two years prior to enrolment); former smoking was indicated when persons stopped smoking before the referent period.

[e] Derived from pre-diagnosis recent body weight (defined as “weight 2 years prior to enrolment”) in kg divided by height in meters squared.

[f] Derived from body weight at age 20 years in kg divided by height in meters squared.

[g] Self-report that diabetes mellitus was diagnosed by a physician, excluding gestational diabetes.

[h] Adjusted for country of data collection (United States; Canada; Australia).

[i] Derived from time since initial colorectal cancer diagnosis divided by number of post-diagnosis surveillance colonoscopies.

[j] P-value for trend: calculated from Cox regression models with ordinal variables as continuous measures.